evident that a great deal can be foretold as to the clinical course of such tumors based on their histologic characters.

Tumors of the brain substance follow the general law governing tumors occurring elsewhere in the body in that the degree of malignancy is greatest in the embryonic cell types, becoming less as cellular differentiation increases. When one realizes that nearly 50 per cent of gliomata are among the fairly well differentiated cell-type tumors and, therefore, of hopeful prognosis following surgery, provided they are accessible in location, one comprehends, in a measure, the importance of recent advances in classification.

Classifications such as Bailey and Cushing have given us, based on the use of highly technical metallic impregnation methods of Cajal, are illuminating and extremely important. It is only by means of these methods that true relationships can be established between the tumor cells and embryonic forms found in the development of normal nervous tissues. These complicated methods are not practicable, however, for the average hospital pathologist. Doctors Courville and Adelstein have met a real need in not only simplifying the classification of Bailey and Cushing, but in making it possible to classify these tumors as to histologic type by means of routine and other relatively simple staining methods. It must be borne in mind, as the authors themselves point out, that this work was possible only after the establishment of these histologic types by means of the more complicated methods.

The result of such simplification will be a stimulation to a more detailed study of the gliomata by the general pathologist as well as by the neuropathologist which over a period of years, will result in an accumulation of a considerable body of new facts and more thoroughly classified knowledge. This new knowledge will in all probability add materially to the benefit of the patient in prolonging his life, will give greater confidence to the neurosurgeon whose lot has been a discouraging one, and will, from a purely scientific standpoint, increase the interest in a subject that has been in the past obscure.

The authors have treated their subject in a simple, intelligent manner. It is decidedly a step forward.

AGRANULOCYTIC ANGINA*

REPORT OF CASE

By GEORGE A. GRAY, M. D.
San Jose

DISCUSSION *by Herbert C. Moffitt, M. D., San Francisco; Ernest H. Falconer, M. D., San Francisco; William H. Strietmann, M. D., Oakland.*

SCHULTZ[1] in 1922 brought to our attention an unusual symptom complex first presented by Schwarz in 1904. The patients with this symptom complex were characterized by gangrenous stomatitis with an unusual blood picture of granulocytic leukopenia. He considered these symptoms manifestations of a specific disease called agranulocytosis or agranulocytic angina. Since that time descriptions of some two hundred similar cases have appeared in medical literature (Friedmann and others).[2] A number of these reports on what was presumably agranulocytosis however, differ distinctly from those which Schultz described under the symptom complex of agranulocytic angina. Because of the increasing frequency with which this condition is being diagnosed, as well as because of its extremely high mortality rate—over 90 per cent usually being fatal—it is desirable to learn as much as we can about this condition by reporting all cases and describing them as fully as possible.

To my mind, several of the patients reported as cured have fallen into the doubtful group, diagnostically speaking, so that to fully test any promising therapeutic suggestions in this rather dismal field we should first be certain that we are dealing with an actual case of true agranulocytosis or agranulocytic angina. To refresh our memories, therefore, a summary of the pertinent points associated with the disease may be here described.

OCCURRENCE AND SYMPTOMATOLOGY

Agranulocytic angina occurs at all ages and in both sexes, but more commonly in females. It is manifested by sudden rise of fever, dysphagia, chills, and malaise. These symptoms progress to severe toxemia and prostration, which, during the course of the disease, become extremely marked. The onset usually comes in a period of good health, but may follow various chronic conditions. The symptomatology is not constant. Stomatitis is nearly always present. There may be regional adenopathy and enlargement of the liver and spleen; while during the course of the disease ulcerations may occur on the throat, vagina, or anus, many of them being membranous in character. Jaundice is common, while petechial hemorrhages are rare except in the rapidly fatal cases.

DIAGNOSIS

The diagnosis is usually made on the blood picture where there is a pronounced leukopenia, and granulocytic leukocytes are either absent or reduced to exceedingly low percentages. The average count is usually 1200 cells per cubic millimeter, although occasionally there may be an initial leukocytosis. During the course of the disease there is a gradual decrease in the number of cells. The percentage of polymorphonuclear leukocytes is always reduced to an average of between zero and six per cent. A relative lymphocytosis is always noted, varying from 60 to 100 per cent. The endothelial cells are from 4 to 8 per cent. The absolute number of lymphocytes is usually decreased, but it may be normal. The degree of anemia is not so severe as that seen in other types of aleukemic forms of myeloses, and lymphadenoses; but the erythrocytes are usually reduced, the count varying between 2,500,000 and 3,500,000. The blood platelets retain a normal count. These blood changes of a neutrophilic leukopenia, with a relative lymphocytoses, are thought to be the result of the primary depressing action of an unknown etiological agent on the bone marrow. A toxin generated by a septicemia, with a special affinity and toxicity for the granulocytic system, is thought to be the active factor in paralyzing this generative function of the bone marrow. The ulcerative sites in the various mucous membranes are thought to arise, secondarily from the blood changes, due to a de-

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* Read before the General Medicine Section of the California Medical Association at the fifty-ninth annual session at Del Monte, April 28 to May 1, 1930.

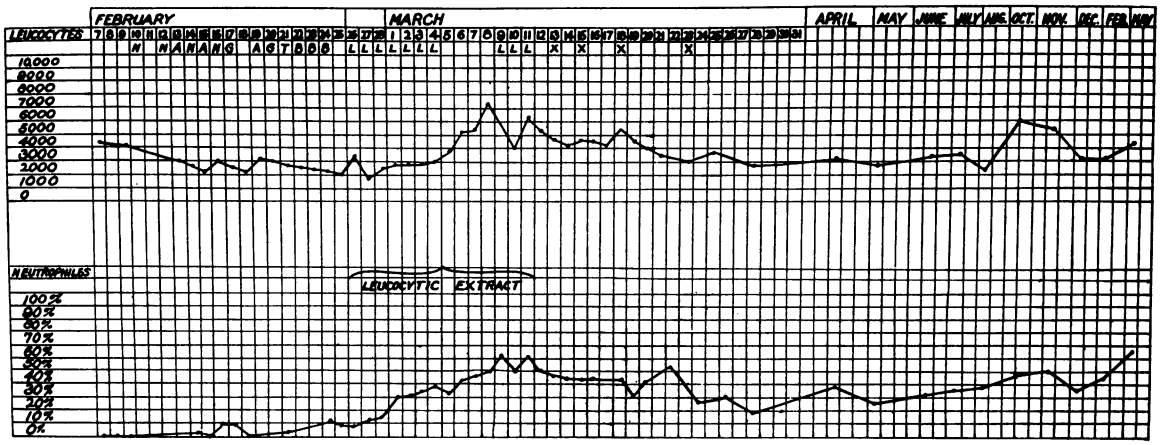

Fig. 1.—Case report chart: N, neoarsphenamin; A, activin milk protein; G, glucose; T, transfusion; B. bacteriophage; L, leucocytic extract; X, roentgen ray.

crease in the body resistance to infection, especially as the ulceration sites show a lack of cellular response of inflammation. The same thing applies to the pneumonic complications in the lungs, which is the usual cause of death. In looking back, therefore, one might wonder if some of our fulminative so-called influenzal pneumonias (with leukopenia) were not in reality cases of agranulocytosis.

ETIOLOGY

The cause of agranulocytosis is still unknown. It is generally accepted that no known microorganism is responsible for the disease. Vincent's organisms are commonly found in the oral cavities of the acute leukopenic patient, especially if there is any necrosis of the mucous membranes; but Vincent's organism may be found in any condition of the mouth where sloughing is taking place. Autopsy findings throw little light on the cause of the disease, as the spleen, lymph glands, and liver show no macroscopic or microscopic changes distinctly peculiar to this condition. Blood culture reports have been rather unconvincing.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in agranulocytic angina usually presents points similar to a reaction to specific poisoning, to leukemia, certain aplastic blood conditions, and to cases of sepsis with a leukopenia.

Since more than 90 per cent of the reported cases have proved fatal, and there is no specific form of treatment available, any therapeutic procedure that has been followed by apparent recovery is deemed of sufficient interest to be worth reporting in detail. Hence, the following citation is reported here: one, because it affords an opportunity of presenting a consecutive picture of the blood changes occurring during the course of a case of apparent recovery of this usually fatal disease; and two, in order that the value of treating these cases with large doses of leukocytic extract may be determined upon by other clinicians.

REPORT OF CASE

Our patient was admitted to the hospital on January 25, 1929, with apparently the symptoms of an acute respiratory infection. Temperature was 103.8 degrees. Pulse rate of 106, and a respiration of 26. Patient complained of aching in the muscles, sore back, backache, soreness in throat, and stuffiness in the nasal passages. Her physical examination was essentially negative, except for evidence of inflamed throat and possibly slight sinus involvement. She complained of headache, frontal in type, and she had given a history of having had some sinus difficulty in the past. Blood count at that time was: hemoglobin, 75 per cent; red blood cells, 4,740,000; leukocytes, 5800; lymphocytes, 24 per cent; monocytes, 67 per cent; and neutrophils, 9 per cent. (Count taken October 29, 1927: leukocytes, 5000; neutrophils, 80 per cent; small lymphocytes, 16 per cent; large mononuclears, 4 per cent.) Under symptomatic treatment her temperature, which on the second day was 101 degrees, gradually subsided to normal on the third day of illness. From that time on it would rise to 99.4 degrees occasionally, but was entirely normal on the thirty-first day of January. On the third day of February, even though temperature arose to 99 degrees in the afternoon, she was permitted to go home. This slight temperature persisted, and on the second day following, flared up to 103 degrees. Temperature varied after readmission from 100 to 103 degrees, until, approximately, March 1, when it again became normal, after thirty-five days of illness.

The most outstanding factors, from a clinical viewpoint, were the marked prostration and the ulcerations that developed in the mouth; these latter being small membranous areas noted along the gums, with the largest on the palate and in the nasopharynx. On the fourth day of the second hospital admission, smears were taken and a typical Vincent's angina spirochete, and fusiform bacilli were reported from the laboratory, while the cultures showed streptococci and staphylococci. We then thought we were dealing with a Vincent's angina and treated it locally with the various procedures used in that disease, but without noticeable effect. Leukocytes, on readmission of February 7, were 4200; lymphocytes, 62 per cent; monocytes, 38 per cent; and no neutrophils. The leukocyte count was gradually reduced to 2400, and the neutrophils varied from 0 to 8 per cent. The lymphocytes ran between 60 and 85 per cent. Intravenous glucose, foreign protein, blood transfusion, and other things were given in an attempt to help overcome the acidosis and prostration, which were the important symptoms during the following days; but without any marked impression upon them. The necrotic areas became more extensive, and in one place extended through to the bony plate of the hard palate, this spot being visible over an area of about one inch in diameter. Cultures were made of this necrotic tissue and when a staphylococcus was found a bacteriophage was obtained. Injections, subcutaneously, of 1, 1½, and 2 cubic centimeters were given daily for three days without any appreciable change in the leukocyte picture, although the neutrophils jumped from 0 per cent up to 11 per cent and then maintained a level at this point before gradually

ascending under subsequent therapy. The second day after the last bacteriophage injection was given, from 10 to 30 cubic centimeters of leukocytic extract were used daily. The necrotic ulcerations were treated locally, the bacteriophage being swabbed on as well as injected under the necrotic layers of the membranes and also directly into them. The improvement of these necrotic areas from day to day was simply miraculous, following the use of the 'phage. The ulcerations and sloughs practically melted away and the other mucous membrane lesions and swellings cleared up very rapidly. Personally, I believe the 'phage was an important factor in the return to normal of the mucous membranes, judging from my observations at the time of administration.

Continuing the leukocytic injections, there was a definite increase in the blood picture, as far as the leukocytes and neutrophils were concerned (see accompanying chart), rising from a low 1600 minimum to a high 7700 maximum in sixteen days, and the neutrophils from 0 to 72 per cent. The patient, however, objected so strenuously to the injections of the leukocytic extract that we were forced to discontinue it. On the fifth day, following the discontinuance of the leukocytic injections, the temperature arose from normal to 100.2 degrees. The leukocytic count dropped from a high point of 6700 to 4000 and the neutrophils from 72 to 52 per cent, and we again proceeded with the leukocytic extract administration. In four days the leukocytes rose to 5500 and the neutrophils to 65 per cent. Here again, due to the objection on the part of the patient to the discomfort resulting from the injections, we again discontinued the administration, resorting at that point to roentgen-ray therapy.[3]

At present the patient looks extremely well and states she feels better than she has in months. Her red blood count is normal and her white blood count, having been taken at regular monthly intervals, was found to vary from 6000 with 46 per cent neutrophils on October 1, 1929, to 4400 and 63 per cent neutrophils on March 24, 1930. The last count on March 24, 1930, was as follows: hemoglobin, 77 per cent; red blood cells, 4,813,000; white blood cells, 4400; neutrophils, 63 per cent; small lymphocytes, 33 per cent; monocytes, 2 per cent; basophils, 2 per cent.

CONCLUSIONS

I believe that in addition to the ordinary symptomatic treatment and the combating of the toxemia in agranulocytosis the most hopeful, present form of therapy is: leukocytic extract in adequately large doses, varying from 20 to 50 cubic centimeters in twenty-four hours, depending upon the granulocytic system response during the acute toxic course of the disease. This to be followed, as soon as the blood picture is held in check, by deep roentgen-ray therapy in one-twentieth skin unit doses over the long bones, as suggested by Friedemann,[2] Call, Gray, and Hodges,[3] and others.[4]

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REFERENCES

1. Schultz. Deutsche med. Wchnschr., Vol. xlviii, 4495, 1922.

2. Friedemann. Ztschr. f. klin. Med., Vol. cviii, 54-56, 1928.

3. Call, Gray, and Hodges. Am. J. Roentgenol., Vol. xx, No. 6, December 1928.

4. For reports of two additional patients with apparent recovery during the use of leukocytic extract, see articles by J. M. Askey, California and Western Medicine, July 1929, Vol. 31, No. 1, pp. 50-51, September 9, 1927 and W. B. Blanton, J. A. M. A., Vol. 92, No. 25, p. 2099, June 22, 1929.

Five patients are also reported as recovered by use of roentgen-ray therapy.

DISCUSSION

HERBERT C. MOFFITT, M. D. (384 Post Street. San Francisco).—Before Schultz published his paper in 1922 we saw several fatal cases of what was then called "aleukemic leukemia" or "sepsis with leukopenia." A young woman seen, with Doctor Jellinek, with, retrospectively, typical agranulocytosis, recovered and remained well. She was given leukocytic extract in moderate doses. Since 1922 I have seen fifteen cases, and only one patient is still living. A woman died during the fifth relapse of ulcerative mouth lesions and typical blood changes. A man, age fifty, with long-standing tabes died with recurrence of throat lesions two years after the initial attack. A woman, age seventy, died in her third attack. Doctor Thayer of Baltimore has recently published notes on an extraordinary case of sore mouth, temperature and agranulocytosis recurring at three-week intervals from birth, or soon after, to the present age of twenty-two. The boy was under my care some years ago. Apparently, with him blood changes preceded temperature and mouth lesions in which Vincent's organisms were constantly present. During one period of agranulocytosis, years before, an intercurrent pneumococcus pneumonia brought about a polynuclear leukocytosis which, after the crisis, gave place to agranulocytosis although the usual periodicity was not due. In the cases which develop right after tooth extraction in apparently healthy individuals, some of whom have had normal blood counts just before, initial infection rather than bone marrow lesions would seem the exciting factor. Moreover, we see the condition apparently following an infection of some chronicity, either in mouth or about the rectum, or even without demonstrable focus. It seems necessary, however, as in Doctor Gray's case, to assume some inherent weakness of bone marrow to explain the lack of the usual reaction to infection. Even now, considering the leukopenia—4400 in his patient—I would not be too enthusiastic about prognosis. If recovery takes place we should insist on careful treatment of existing infections, although radical measures in regard to teeth and tonsils should be avoided if possible. I would lay more stress upon Vincent's disease than is usually done. It often lies dormant deep in the gums, and we may safely use bismuth preparations if we fear arsphenamin. Doctor Gray has given the best methods of treatment we have at command during the acute stages. I would add massive doses of liver extract and a fixation abscess by injection of one or two cubic centimeters of turpentine deep into the anterior thigh muscles. If patients apparently recover, they should be tested for achylia, chronic infections should be treated, diets rich in nucleins, liver would seem in order, and frequent blood counts should determine the efficacy of sun or quartz-lamp treatments or the advantage of bone marrow, arsenic or other drug administration.

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ERNEST H. FALCONER, M. D. (384 Post Street, San Francisco).—One is particularly interested in Doctor Gray's carefully prepared report on account of the apparently increasing frequency of this syndrome. It is a moot question whether the so-called agranulocytic angina described by Schultz in 1922 is a distinct clinical entity or a group of diseases. I have recently seen a case in a child which, clinically, fitted very closely into the syndrome known as agranulocytic angina, but which followed closely an attack of measles. Measles is, of course, one of the diseases that produces a leukopenia and low granulocyte count. There are many variants of the originally described syndrome reported in the literature. Until we know more of the etiology, therapy must of necessity be empirical. This is no reason, however, for not making careful observations, as Doctor Gray has done, on the results following the use of leukocytic extract. Others are reporting results similar to Doctor Gray's, and we await with interest reports of experimental work with this agent. One wishes that Doctor Gray had mentioned the brand of leukocytic extract used and the method of its preparation.

WILLIAM H. STRIETMANN, M. D. (230 Grand Avenue, Oakland).—Doctor Moffitt has referred to a young man with a cystic recurrence of agranulocytosis, associated with a recurrent exacerbation of a stomatitis and especially gingivitis of moderate grade. I have had the opportunity to observe this same patient for the past two years. His "attacks" recur at six-week intervals, but are growing much less severe. The fever does not now exceed 100 degrees, and is often lower. The mouth symptoms are less severe and the leukocyte count may not go below 3000, though the granular elements are always notably reduced, varying in the past two years from 35 to 5 per cent during the height of the exacerbation. This young man was originally the patient of Dr. William S. Thayer and, from recent correspondence with him, I am quite sure that the case will be fully reported in Johns Hopkins bulletin.

Arsenicals must be used with caution because of the tendency to produce a leukopenia.

Of three cases under my observation in the past few years, none have recovered. One of these was treated, according to Doctor Gray's suggestions, with 20 cubic centimeters of leukocytic extract at eight-hour intervals, supplemented by a blood transfusion, but died on the third day.

Again, one should always bear in mind the tendency to recur, remissions of a variable period being not uncommonly noted.

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DOCTOR GRAY (Closing).—Further blood counts on this patient have been checked through the present year. On May 1930: leukocytes, 6900; neutrophils, 62 per cent. On July 1930: leukocytes, 5900; small lymphocytes, 45 per cent; eosinophils, 4 per cent; basophils, 2 per cent; neutrophils, 49 per cent. On September 1930: leukocytes, 3800; small lymphocytes, 15½ per cent; monocytes, 10½ per cent; neutrophils, 47 per cent (200 cells counted). On November 1930: leukocytes, 3050; red blood corpuscles, 4,310,000; hemoglobin, 84 per cent; small lymphocytes, 47 per cent; monocytes, 2 per cent; neutrophils, 51 per cent.

The patient is still feeling perfectly well and has recently had a slight cold, which may have been a factor in depressing the last two leukocyte counts. Because of this gradual drop, I have again started leukocytic extract injections in two cubic centimeter amounts twice weekly, and the patient is now feeling better symptomatically, as regards her strength, energy, etc. The blood count, after four injections, is as follows: On December 5, 1930—leukocytes, 3900; neutrophils, 42 per cent; lymphocytes, 45 per cent; mononuclears, 2 per cent; basophils, 1 per cent.

Regarding Doctor Faulkner's question as to the brand of leukocytic extract used and the method of its preparation, I wish to state that I used the stock preparations of the Vitalait Laboratories, San Francisco, and the E. R. Squibb & Sons, New York.

Since reporting this case at the fifty-ninth annual session at Del Monte, I have been in consultation on three other cases of agranulocytosis; two of which were of such a fulminating character that they expired within twenty-four hours of the time of diagnosis. This was, naturally, before leukocytic extract had any possible chance of being of value. One case in a child less than two years of age was treated with leukocytic extract in adequate dosage with remission of attacks; but eventually the child expired during a relapse when no leukocyytic extract was used. There was some doubt as to this being a true agranulocytosis, but because of the severe primary anemia present, which yielded somewhat, for a period at least, to repeated transfusions, this case was thought to be an aplastic anemia with accompanying leukopenia rather than a true agranulocytosis.

It is hoped that this case report will stimulate others to use the massive dosage of leukocytic extract so that the real efficacy of this treatment may stand or fall under an adequate clinical trial.

ARTHRITIS*

By RODNEY F. ATSATT, M. D.
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DISCUSSION *by William J. Kerr, M. D., San Francisco; John C. Wilson, M. D., Los Angeles.*

IT may seem presuming for an orthopedic surgeon to address the medical section on the subject of arthritis, but it will be my endeavor to present the matter from the point of view of an orthopedist with the hope that it may be of some value to you.

Each specialist attacks problems in medicine according to his training and train of thought and, in so doing, each one is apt to lose sight of the fact that the symptoms which he treats are but a portion of a general disease picture. The internist may interpret the disease in terms of diet, medication, and disturbances of bowel regulation. The rhinolaryngologist and the dentist think of it as one caused by focal infections. The gynecologist and the urologist may also recognize the disease as one based on focal infection. The orthopedist sees end results with the problems of contractures and malfunctioning joints and further may think in terms of posture, statics and poor body mechanics as factors influencing the course of the disease. The physiotherapist may see the disease as a problem of blood and lymph stasis, bowel stasis, atrophied muscles, adherent tendons, fibrotic capsules, and far too often there is the *bete noir* of *contractures*. Thus we have ofttimes a multiplicity of investigation and therapy without much thought being given to the patient as a whole. It is the thesis of this paper that consideration of the patient as an entity is probably the most important item in the treatment of arthritis.

A DISEASE OF ANTIQUITY

Let us review briefly some of the knowledge of the subject. The disease is of tremendous antiquity, for paleontologists working in Rancho La Brea here in California have brought to light specimens of saber-toothed tigers in which the spines show well-developed hypertrophic arthritis. From this early prehistoric period arthritis may be traced to ancient Egypt, which knew the disability as one of middle and old age, as has been shown by dissection and roentgenograms of mummy specimens. The Greeks and Romans treated arthritis by means of baths and purges. Recent years, however, have seen a determined effort on the part of clinicians and research workers to solve what is probably one of the most widespread and yet one of the most baffling of diseases.

CLASSIFICATION

The most satisfactory classification is the old one which recently has been adopted by the American Committee for the Control of Rheuma-

* Read before the General Medicine Section of the California Medical Association at the fifty-ninth annual session at Del Monte, April 28 to May 1, 1930.